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Cytogenetic and Clinical Findings in a Patient With a Deletion of 16q23.1: First Report of Bilateral Cataracts and a 16q Deletion

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The most commonly reported manifestations of 16q deletions are severe growth and developmental disorders and anomalies of the craniofacial, visceral, and musculoskeletal systems. We reviewed the findings of patients reported with 16q- syndrome and compared them to our patient, a 4½-year-old boy with a deletion of 16q23.1. Findings include psychomotor retardation, hypotonia, high forehead, hypertelorism, upslanting palpebral fissures, low-set abnormally modeled ears, and talipes equinovarus. Anomalies present in our patient not reported in others with 16q- syndrome include bilateral cataracts, iris coloboma, and autistic-like behavior. It is of note that a locus for autosomal dominant congenital cataract, known as Marner cataract, was mapped previously to 16q22. Because our patient has bilateral cataracts and a unilateral iris coloboma, it seems likely that a gene involved in ocular development is located within 16q23.1. Our patient's deletion may also include the gene involved in Marner cataract and may further assist in the isolation of this gene. Am. J. Med. Genet. 73:180–183, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: cataracts; 16q23.1; deletion syndrome

INTRODUCTION

At least 25 patients with interstitial long arm deletions of chromosome 16 have been reported. Most have growth delay, microcephaly, failure to thrive, hypotonia, mental retardation, large anterior fontanel, prominent metopic suture, high forehead, hypertelorism, short and/or upslanting palpebral fissures, broad and/or flat nasal bridge, and low-set and/or abnormal ears. Some patients have congenital heart defects and renal malformations. Musculoskeletal findings include a short neck, narrow thorax, malpositioned toes or talipes equinovarus, and a broad first toe. The segments 16q12q13 [Elder et al., 1984; Hoo et al., 1985], 16q21 [Fryns et al., 1977, 1979; Lin et al., 1983; Naritomi et al., 1988; Edelhoff et al., 1991; Rivera et al., 1985] and 16q22.1 [Fujiwara et al., 1992] have been suggested as critical bands for this deletion syndrome. We report a 4½-year-old boy with a deletion of band 16q23.1, findings of 16q- syndrome, and a previously unreported finding, bilateral cataracts.

CLINICAL REPORT

The patient was the third child born to a 33-year-old Hispanic mother and a 41-year-old Hispanic father. No consanguinity was identified. His two sibs, age 15 and 18 years, are physically and developmentally normal. There were no known teratogen exposures. Following an unremarkable pregnancy, the patient was born at term by spontaneous vaginal delivery. Birth weight was 3,487 g, birth length 49.5 cm, and head circumference (OFC) was 35.6 cm (all appropriate for gestational age). Apgar scores were 9 and 9 at 1 and 5 min, respectively.

On examination at age 4½ years, his height was 104 cm (25th centile), weight 18.1 kg (50th centile), and OFC 53.5 cm (90–97th centile). There was no craniosynostosis. The hairline was low-set above a high forehead. His ears were low-set, abnormally modeled, and slightly posteriorly angulated, measuring 5 cm (between the 3rd and 25th centile) in length (Fig. 1). The left pupil was round, regular, and reacted to light. There was an inferior coloboma of the right iris. Bilateral cataracts were present and visualized as diffuse milky clouding of both lenses with several small droplike precipitates of white material in each lens. There was synophorys. There was hypertelorism with the outer canthal distance measuring 10 cm (>2SD) and the inner canthal distance measuring 3 cm (+1SD). Palpebral fissures were upslanting and long, measuring 3.5 cm (>>2SD). Genitalia were normal. Palmar creases and digits were normal. There was talipes equinovarus.

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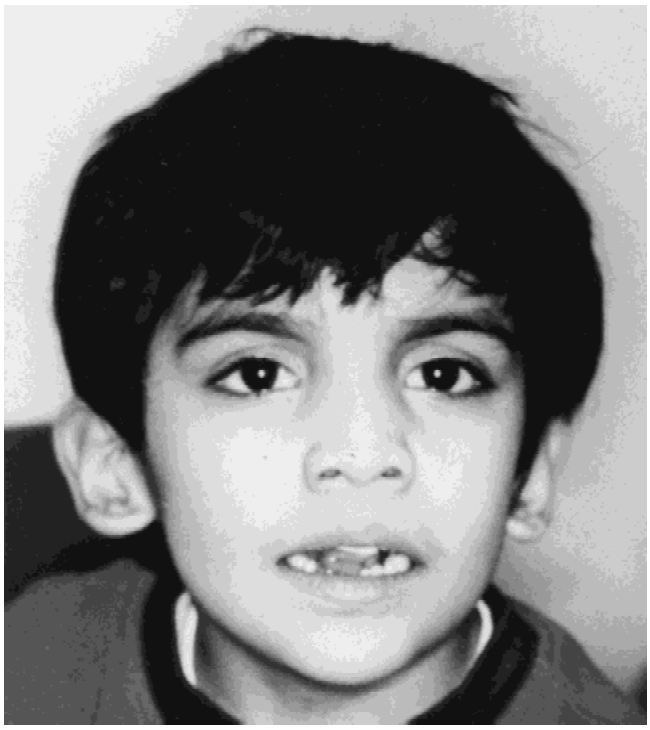

Fig. 1. Patient at age 4½ years. Note the low-set hairline, high forehead, low-set and posteriorly rotated ears, synophorys, hypertelorism, and long, upslanting palpebral fissures.

The patient's psychomotor development was delayed, but there was no regression. He began using words at 1 year; however, he was just beginning to put 3 and 4 words together at the age of 4½ years. He walked at 16 months and was toilet trained at 3 years. At the age of 4$^{4}/_{12}$ years his composite score was 59 on the Revised Stanford-Binet Intelligence Scale (4th Edition). He was functioning at the low end of the mildly mentally impaired range, with a mental age equivalency between 24 and 26 months. He displayed some autistic-like behaviors, including repetitive and independent play and very little eye contact. He did not exhibit hand flapping or waving gestures. He had a short attention span but a good memory. Neurological examination showed mild central hypotonia and some mild spasticity at the ankles with reducible contracture. An EEG did not show paroxysmal activity, but did show slowing of background activity indicative of an encephalopathy. A brain MRI was normal. Deep tendon reflexes were slightly increased but symmetric. There were no sensory deficits or tremor noted. Intermittently, the patient walked on his toes.

Metabolic studies revealed a slightly decreased pyruvate and a nondiagnostic organic acid profile with 2-ketoglutaric acid and suberin. Lactate and carnitine levels were normal. Plasmid amino acid screen was normal.

Evaluation of prometaphase chromosomes demonstrated a 46,XY,del(16)(q22.3q23.2) karyotype (Fig. 2). Parental chromosomes were normal. Fluorescent in situ hybridization (FISH) using a chromosome 16 paint showed signal only over the two chromosome 16 homologs, ruling out the possibility that the deleted segment was translocated to another location. FISH, using a probe specific for chromosome 16 telomeric sequences, hybridized to both chromosome 16 homologs, indicating that the deletion was interstitial.

DISCUSSION

The most commonly reported manifestations of 16q deletions are severe growth and developmental disorders, and multiple minor anomalies of the craniofacial,

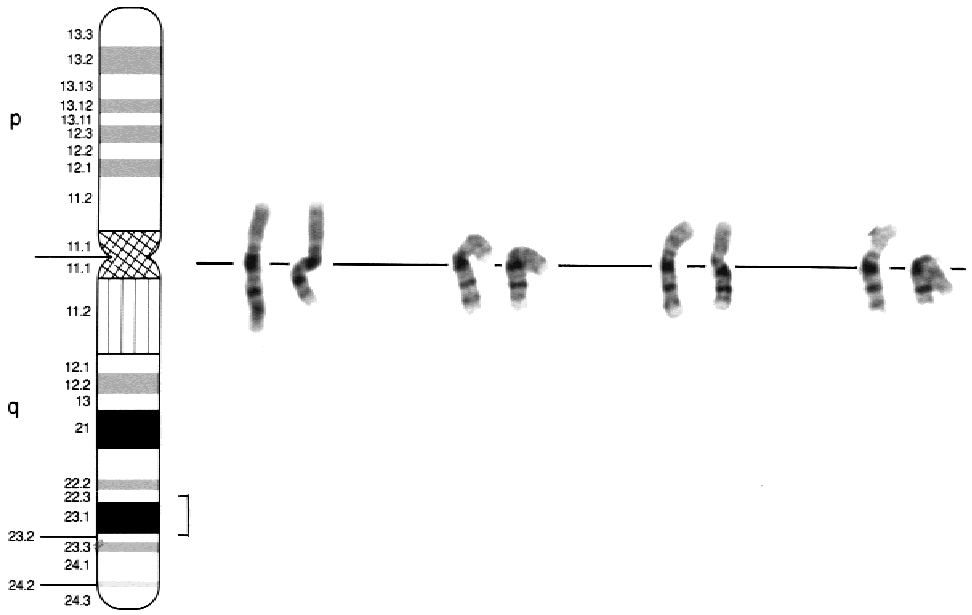

Fig. 2. An idiogram of chromosome 16 indicates the segment that was deleted. Four pairs of chromosome 16s from the patient are provided to illustrate the deletion. Normal homologue (left) and deleted 16q23.1 band (right).

visceral, and musculoskeletal systems. We reviewed the manifestations of 23 patients with 16q- syndrome and compared them to those in our patient (Table I). Findings include psychomotor retardation, central hypotonia, high forehead, hypertelorism and upslanting palpebral fissures, low-set abnormally modeled ears, and talipes. Anomalies present in our patient but not reported in others with 16q abnormalities include cataracts, iris coloboma, and autistic-like behaviors. There are 5 reported patients with structural chromosome abnormalities similar to our patient's deletion [Rivera et al., 1985; Cooke et al., 1987; Ionasescu et al., 1987; Fujiwara et al., 1992; Callen et al., 1993]. We compared them to our patient (Table I). Only one of these deletions, 16q22.1q24.1, [Callen et al., 1993] encompasses our patient's deletion. This female patient had developmental and growth delays but few minor anomalies. While not reported in patients with an isolated 16q deletion, cataracts were reported by Ionasescu et al. [1987] in a patient with a 46,XY,rec(16)dup(16p)inv(16)(p13.1q22) karyotype (which includes 16q22-qter deficiency). He had growth and development delays, and craniofacial and musculoskeletal abnormalities characteristic of 16q- syndrome. In addition, the patient had myopathy, hearing loss, and seizures. It is not known if the cataracts resulted from the duplication on the short arm or the deletion on the long arm. A gene for congenital cataracts with microphthalmia has been localized to 16p13.3 [Yokoyama et al., 1992], but Ionasescu et al. did not report microphthalmia in their patient.

While the cause of most congenital cataracts is unclear, some known causes include prenatal exposures to X-irradiation, corticosteroids and sulfonamides, intrauterine infection (rubella, herpes, and mumps), maternal diabetes and malnutrition, and fetal galactosemia [Nelson and Ullman, 1995]. No such maternal exposures were noted in our patient.

Among the genes mapped to the long arm of chromosome 16 is a gene for congenital cataract, first studied by Marner [1949] in a large Danish kindred. Marner cataract was linked to haptoglobin, at band 16q22 by linkage analysis [Eiberg et al., 1988; Marner et al., 1989]. Marner cataract manifests as progressive opacities at the Y-sutures of the lens. Most of the cataracts are zonular, but some are also nuclear, anterior polar,

TABLE I. Clinical Features of 16q-Syndrome and Comparison of Present Case With Previously Reported Cases Involving Overlapping Deletions (q22.1q24.1) and More Proximal Deletions (q11.1q22)*

16q segment involved	q22.3q23.2[a]	q22.1-q24.1[b–e]	q11.1-q22[e–q]
Number of cases	1	5	18
Growth and development			
Small for gestational age	−	2/5[r]	8/17[r]
Postnatal growth retardation	−	3/4	16/18
Microcephaly	−	4/5	10/18
Mental retardation	+	4/4	16/16
Failure to thrive	−	4/4	16/16
Hypotonia	+	3/4	16/16
Craniofacial			
Large anterior fontanelle	−	3/5	13/13
Split sutures	−	1/4	9/13
Prominent metopic suture	−	2/4	10/15
High forehead	+	5/5	14/17
Hypertelorism	+	4/5	10/18
Short palpebral fissures	−	2/3	7/18
Upslanting palpebral fissures	+	2/3	6/18
Broad, flat nasal bridge	−	2/5	14/18
Low-set, dysmorphic ears	+	4/5	18/18
Micrognathia	−	3/5	10/18
High arched/cleft palate	−	4/5	13/16
Visceral			
Congenital heart defect	−	1/4	8/18
Ectopic anus	−	0/3	5/15
Renal cystic dysplasia	−	0/3	5/13
Musculoskeletal			
Short neck	−	2/3	11/13
Narrow thorax	−	1/3	8/15
Flexed fingers	−	1/2	7/13
Bilateral simian creases	−	1/3	6/13
Malpositioned toes	−	1/2	8/13
Talipes equinovarus/calcaneovalgus	+	1/3	6/14
Broad first toe	−	2/2	12/16

*Adapted from Lin et al. [1983].
[a]Present case; [b]Rivera et al. [1985]; [c]Ionasescu et al. [1987]; [d]Fujiwara et al. [1992]; [e]Callen et al. [1993]; [f]Fryns et al. [1977]; [g]Taysi et al. [1978]; [h]Fryns et al. [1979]; [i]Fryns et al. [1981]; [j]Lin et al. [1983]; [k]Elder et al. [1984]; [l]Hoo et al. [1985]; [m]Cooke et al. [1987]; [n]Krauss et al. [1987]; [o]Naritomi et al. [1988]; [p]Casamassima et al. [1990]; [q]Edelhoff et al. [1991].
[r]Denotes total number of patients in which this physical finding was reported.

and stellate cataracts. The cataract is inherited in an autosomal dominant manner with complete penetrance and intrafamilial variability. In affected individuals, each lens can have different degrees of opacity. The morphology of the cataracts in our patient was not able to be ascertained. Although Marner cataract is localized to 16q22, it is possible that the gene is actually located within the segment that is deleted in our patient.

Patients with 16q- syndrome have been reported with deletions ranging from 16q11.1 [Krauss et al., 1987] to 16q22.3 [Fujiwara et al., 1992]. Although no obvious phenotype karyotype correlation has emerged, patients with more distal deletions may in general have a more severe phenotype [Callen et al., 1993]. It may be possible that genes residing in proximal 16q influence specific phenotypes (i.e., split sutures and visceral abnormalities) and in the overlapping segment (16q22) that most of the 16q- patients appear to share (i.e., high forehead, high arched/cleft palate, and broad first toe) (Table 1). However, so far no specific phenotypic anomalies can be assigned distal to 16q22.

In summary, our patient has mental retardation with autistic-like behavior, minor anomalies, unilateral iris coloboma, and bilateral congenital cataracts. Ocular anomalies such as coloboma are often associated with congenital cataracts [Luntz, 1995]. While a patient with a 16q deletion was reported with cataracts, he also had a duplication on the short arm of chromosome 16. We are unaware of any patient with only a 16q deletion and cataracts, and no patient with a 16q chromosome aberration has been reported with iris coloboma. It is possible that a gene encoding a protein involved in ocular development is located between 16q22.3 and 16q23.2. Our patient's deletion may also include the gene for Marner cataract and further assist in the localization of this gene.

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